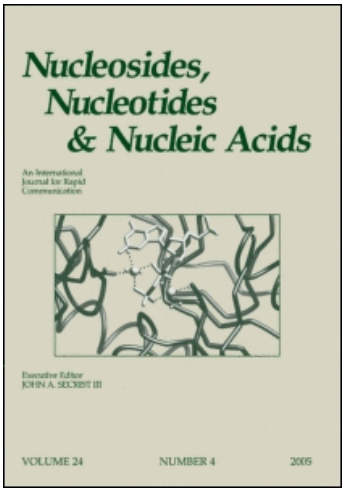

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Kocalka, Petr , Pohl, Radek , Rejman, Dominik and Rosenberg, Ivan(2005) 'Synthesis of Racemic and Enantiomeric 3-Pyrrolidinyl Derivatives of Purine and Pyrimidine Nucleobases', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 805 — 808
To link to this Article: DOI: 10.1081/NCN-200060287
URL: http://dx.doi.org/10.1081/NCN-200060287

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):805–808, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200060287

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SYNTHESIS OF RACEMIC AND ENANTIOMERIC 3-PYRROLIDINYL DERIVATIVES OF PURINE AND PYRIMIDINE NUCLEOBASES

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□ *The present work relates to the synthesis of pyrrolidine nucleoside analogs. Starting from malic acid, we have elaborated a high-yield synthesis of racemic and enantiomeric N-protected 3-pyrrolidinols and their O-mesyl derivatives as key compounds for alkylations of purine and pyrimidine nucleobases. On varying base and solvent, we have found conditions providing both satisfactory N-/O-regioisomeric ratio and acceptable yield for pyrimidine compounds.*

Keywords *N*-Protected 3-Pyrrolidinols, Pyrimidines, Purines, *O*,*N*-Alkylation, Pyrrolidine Nucleosides

INTRODUCTION

Sugar-modified nucleoside analogs are important group of antimetabolites exhibiting, in many cases, remarkable antiviral and anticancer properties. Biological activity of these compounds, acting mostly as chain terminators in DNA polymerase catalysed polymerisation, is determined by their gradual in vivo phosphorylation to nucleoside triphosphate analogs. The search for novel nucleoside and nucleotide analogs capable of discriminating between cellular and viral/tumor enzymes of nucleic acid metabolism is therefore highly desirable.

RESULTS AND DISCUSSION

The Mitsunobu alkylation performed with 6-chloropurine and (3*S*)-*N*-benzyl-3-hydroxypyrrolidine (**1**) provided a good yield of desired compound **2a** (Scheme 1).

Support by grants #203/02/D150 (GA Czech Republic) and #A4055101 (GA AS Czech Republic) under research project Z4055905 is gratefully acknowledged. Authors are indebted to Dr. Zdenek Tocik (Group of Oligonucleotides) for valuable discussion, and to the staff of the Department of Mass Spectroscopy, Dr. Kvetoslava Kertisova, Dr. Blanka Kralova, and Dr. Karel Ubik (Head) for measurements of HR-MS. The excellent technical assistance of Dr. Petr Simek and Mr. Jiri Strnad, both of Service Laboratories of this Institute, is also gratefully acknowledged.

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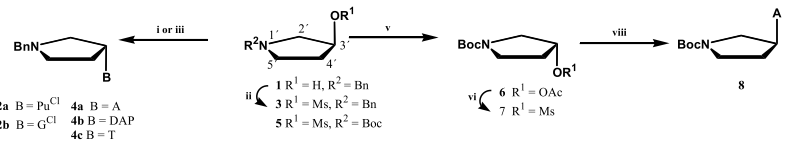


(**i**) **1**, 6-chloropurine or 2-amino-6-chloropurine, Ph_3P, DEAD, THF; (**ii**) MsCl, pyridine, DCM; (**iii**) **3**, adenine, 2,6-diaminopurine or thymine, DMSO, Cs_2CO_3; (**v**) **5**, AcONa, DMF; (**vi**) a) sat. NH_3 in MeOH; b) MsCl, pyridine, DCM; (**viii**) a) **7**, adenine, DMSO, Cs_2CO_3;

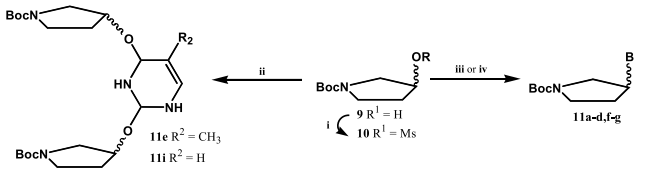
SCHEME 1 Synthesis of (*S*)-configured nucleoside analogs.

Under similar conditions, however, the reaction of 2-amino-6-chloropurine with **1** failed, giving a mixture of products in which expected derivative **2b** was not detected. On the contrary, *N*-Boc-3-hydroxypyrrolidine (**9**) (Scheme 2) reacted smoothly with 2-amino-6-chloropurine to yield, after treatment with alkali, guanine nucleoside **11b**. Concerning the Mitsunobu alkylation of pyrimidines, described method[1] providing 1-*N*-substituted pyrimidines from uracil or thymine and *N*-benzyl-3-hydroxypyrrolidine (**1**) completely failed; we obtained no product. The Mitsunobu reaction performed with *N*-Boc-3-hydroxypyrrolidine (**9**) (Scheme 2), however, yielded exclusively the respective 2,4-*O*-disubstituted thymine **11e** and uracil **11i** derivatives, as determined from H,C-heterocorrelated NMR spectra (Table 1). Also in this case no significant amounts of 1-*N*-substituted pyrimidines were detected.

In the light of these findings we turned our attention to alkylation reaction employing mesyloxy group in nucleophilic displacement. Reaction of adenine, 2,6-diaminopurine, or thymine with (3*S*)-*N*-benzyl-3-mesyloxypyrrolidine (**3**) led unexpectedly to very low yields of pyrrolidine nucleosides **4a–c**. In this case, intramolecular alkylation reaction on the pyrrolidine nitrogen and/or β-elimination of mesyloxy group in compound **3** probably took place instead of nucleophilic displacement of the mesyloxy group by nucleobase.

To eliminate the basicity of the nitrogen atom in pyrrolidine compounds **1** and **3**, we replaced *N*-benzyl group for *N*-Boc. Thus, (3*S*)-*N*-Boc-3-mesyloxypyrrolidine (**5**) (Scheme 1) was converted via acetyl derivative **6** to (3*R*)-*N*-Boc-3-mesyloxypyrrolidine (**7**). The reaction of this compound with adenine provided nucleoside **8** in excellent yield (70%).

The results of nucleobase alkylation with racemic mesyl derivative **10** under various conditions are summarized in Table 2. The alkylation of adenine and



(**i**) MsCl, pyridine, DCM; (**ii**) **9**, thymine, uracil or 2-amino-6-chloropurine, Ph_3P, DEAD, dioxane;
(**iii**) **9**, 2-amino-6-chloropurine, Ph_3P, DIAD, THF;
(**iv**) a) **10**, **B** according to the Table I;

SCHEME 2 Synthesis of racemic nucleoside analogs.

TABLE 1 NMR and MS Data for Pyrimidine Nucleosides

Nucleoside		HR-MS		Selected ^{13}C chemical shifts (ppm)				
		Calcd.	Found	CH-base	C-2	C-4	C-5	C-6
T	**11d**	295.164382	295.166461	53.52	151.08	163.79	109.43	137.56
T^{OO}	**11e**	467.286960	467.288505	75.18, 76.05	162.36	168.07	111.24	158.00
C	**11f**	281.160317	281.161366	54.66	155.58	165.40	93.82	142.17
C^{O}	**11g**	281.160317	281.161215	73.92	164.17	165.46	99.58	156.17
U	**11h**	282.146611	282.145381	54.16	151.19	163.32	101.81	142.15
U^{OO}	**11i**	453.271310	453.272721	75.51, 75.34	163.90	170.09	102.79	159.73

2,6-diaminopurine with mesyl derivative **10** (Scheme 2) proceeded smoothly in DMSO in the presence of Cs_2CO_3 as a base to yield 9-substituted compounds **11a**, **11c**. The alkylation of pyrimidine bases with mesyl derivative **10** afforded, in moderate yield, a mixture of *N*- and *O*-regioisomers,[2] in which *O*-alkylated derivative was present in a relatively high amount. On varying the base and solvent combination, we have found conditions providing both satisfactory *N*-/*O*-regioisomeric ratio and acceptable yields. Similar results were obtained with enantiomerically pure mesyl derivatives **5** and **7**.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 500 spectrometer (^{1}H at 500 MHz, ^{13}C at 125.8 MHz) in DMSO-d_6 and were referenced to the solvent signal ($\delta H = 2.50$, $\delta C = 39.7$). Mass spectra were recorded on ZAB-EQ (VG Analytical) instrument, using FAB (ionization with Xe, accelerating voltage 8 kV). Glycerol and thioglycerol were used as matrices.

General Method for Alkylations (Table 2): The appropriate nucleobase was dried in vacuo at 50–100°C for 16 h. To the stirred suspension of nucleobase in DMSO or DMF (5 mL/mmol) under argon atmosphere, Cs_2CO_3 or NaH (1 eq) was added and the suspension was stirred at 100°C for 20 min. The solution of mesyl derivative **10** (1 eq) in the same solvent (5 mL/mmol) was added. After completion

TABLE 2 Yields of Nucleobase Alkylation (%)

Conditions	A (**11a**)	G* (**11b**)	DAP (**11c**)	T (**11d**)	T^{OO} (**11e**)	C (**11f**)[2]	C^{O} (**11g**)[2]	U (**11h**)	U^{OO} (**11i**)
DMF-Cs_2CO_3	49	14	50	22	14	23	49	17	13
DMSO-Cs_2CO_3	71	ND	76	26	<5	18	24	ND	ND
DMF-NaH	ND	ND	ND	28	10	ND	ND	ND	ND
DMSO-NaH	ND	ND	ND	40	<5	54	39	32	10

A–adenin-9-yl, G–guanin-9-yl, DAP–2,6-diaminopurin-9-yl, T–thymin-1-yl, T^{OO}–thymin-2,4-*O*-diyl, C–cytosin-1-yl, C^{O}–cytosin-2-*O*-yl, U–uracil-1-yl, U^{OO}–uracil-2,4-*O*-diyl, Pu^{Cl}–6-chloropurin-9-yl.

*Compound was obtained after hydrolysis of 2-amino-6-chloropurine derivative with 1 M sodium hydroxide in *aq* dioxane.

of reaction the mixture was concentrated, adsorbed onto a column of silica gel, and the compound was eluted by a linear gradient of ethanol in chloroform. For charaterization see Table 1.

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